Indian Journal of Chemistry
Vol. 37B, February 1998, pp. 167 - 171

Note

Preparation of some 5,7-diarylcyclohexeno[3,4-*d*]-1-selena-2,3-diazolyl-6-spiro-5'-(2',3'-pyrazolidine / 2',3'-oxazolidine)-1',4'-diones and 5,7-diarylcyclohexeno[3,4-*d*]-1-thia-2,3-diazolyl-6-spiro-5'(2',3'-pyrazolidine/2',3'-oxazolidine)-1',4'-diones

D Bhaskar Reddy*, M V Ramana Reddy & V Padmavathi

Department of Chemistry, Sri Venkateswara University, Tirupati 517 502, India

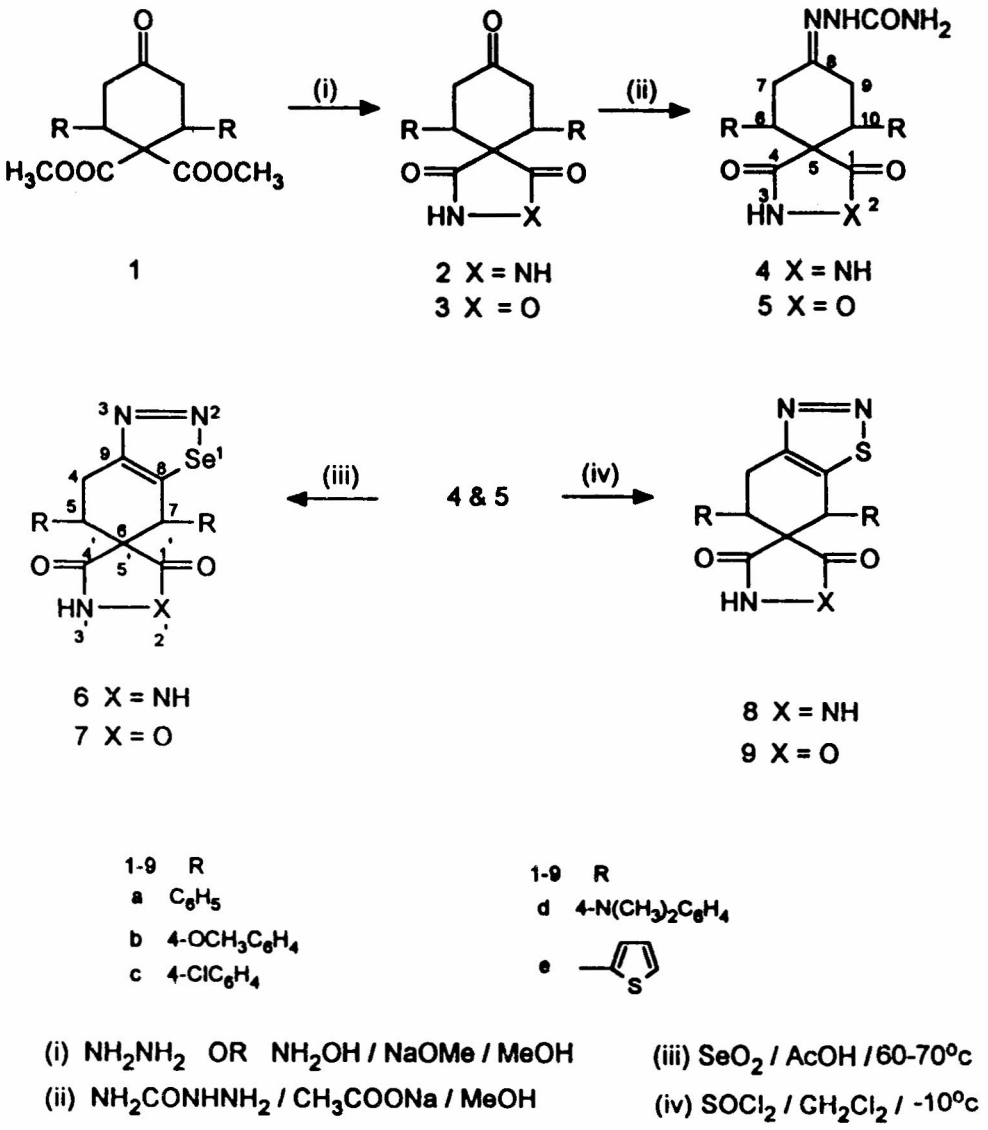
Received 15 May 1997; accepted (revised) 11 November 1997

Synthesis of the title compounds has been accomplished through dimethyl-2,6-diaryl-4-oxocyclohexane-1,1-dicarboxylates **1**. The latter on condensation with $NH_2NH_2.H_2O$ and $NH_2OH.HCl$ give 6,10-diaryl-2,3-diazaspiro(4,5)decane-1,4,8-triones and 6,10-diaryl-2-oxa-3-azaspiro(4,5)decane-1,4,8-triones **2** and **3**. The semicarbazones **4** and **5** of **2** and **3** on reaction with SeO_2 and $SOCl_2$ give 5,7-diaryl cyclohexeno[3,4-*d*]-1-selena-2, 3-diazolyl-6-spiro-5'-(2', 3'-pyrazolidine/2', 3'-oxazolidine)-1',4'-diones **6,7** and 5,7-diaryl cyclohexeno[3,4-*d*]-1-thia-2,3-diazolyl-6-spiro-5'-(2', 3'-pyrazolidine/2',3'-oxazolidine)-1',4'-diones **8,9**. The IR and NMR spectral data correlate to the structures of all the new compounds.

We have been extensively investigating the synthetic potential of dimethyl-2,6-diaryl-4-oxocyclohexane-1,1-dicarboxylates **1** as a source of a variety of heterocyclic systems[1-4]. It is well known that a number of heterocyclic compounds containing nitrogen and sulfur possess different pharmacophoric properties. However, reports about selenium containing heterocycles are relatively less[5-7], although some of them are used as chemotherapeutic agents[8,9]. In continuation of our ongoing programme it is felt desirable to incorporate sulfur/selenium as hetero atoms so that a new class of condensed spiro-heterocycles having 2,3-pyrazolidine/2,3-oxazolidine-dione moieties in combination with 1-selena/1-thia-2,3-diazoles could be obtained.

Infact, the synthetic intermediates[10] **1** have been obtained by the Michael addition of dimethyl malonate to 1,5-diaryl-1,4-pentadien-3-ones. The 6, 10-diaryl-2, 3-diazaspiro-(45)decane-1 4 8-triones **2** and 6,10-diaryl-2-oxa-3-azaspiro-(4,5)decane-1,4,8-triones **3** have been prepared on condensation of **1** with hydrazine hydrate and hydroxylamine hydrochloride, respectively[3,4]. The carbonyl group of **2** and **3** is exploited to construct 1-selena/1-thia-2,3-diazoles. This has been achieved by the condensation of **2/3** with semicarbazide hydrochloride to get semicarbazones **4/5** of **2/3**. The IR spectrum (ν_{max} cm^{-1}) of **4** showed absorption bands at 1675 and 3200 (C=O and NH) of pyrazolidinedione moiety and at 3245 (*NH*CO), 3450 (CO*NH*$_2$), 1660 (*CO*NH$_2$) and 1450 (C=N) of semicarbazone moiety. The absence of a band at 1700 for carbonyl group of cyclohexanone confirms the formation of **4**. The compound **5** also exhibited absorption bands nearly in the similar regions. Besides this, it also exhibited band in the region 1780 (C=O of 2,3-oxazolidinedione). Compounds **4** and **5** on cyclization with SeO_2 and $SOCl_2$ gave **6/7** and **8/9**, respectively. The absence of bands corresponding to semicarbazone unit in **6-9** and the presence of bands due to N=N (1520-1545) in **6-9** and C-S (690-700) in **8** and **9** confirms that the cyclization indeed has taken place in **4** and **5** (see Scheme I, Table I).

The ^1H NMR spectra (δ, ppm) of **4** and **5** can be rationalized by presuming that the two aryl groups at 6 and 10 positions are in true *cis*-1,3-arrangement in the preferred rigid chair conformation of cyclohexane moiety[3,4], although number of dynamic forms do exist. The methine (H_A) and methylene (H_M and H_X) protons of **4** and **5** constitute AMX splitting pattern. The H_A due to coupling with H_M and H_X appears as a doublet of doublet in the downfield region. The H_M due to geminal and vicinal couplings also appear as a doublet of doublet in between H_A and H_X. The H_X also experiences a similar effect and display a doublet of doublet in slightly upfield region of the spectrum. A broad singlet for NH is observed not only in **4** but also in **5**. However, the resonance



Scheme I

signal for NH_2 is merged with aromatic protons as is evidenced by its disappearance on exchange with D_2O. The NH of 2,3- pyrazolidinedione and 2,3-oxazolidinedione in **4** and **5** appeared as a singlet. The ^1H NMR spectra of **6-9** exhibited three sets of signals for methine (C_5-H and C_7-H) and methylene (C_4-H) protons of cyclohexene unit. The C_7-H appears as a singlet while C_5-H a triplet and C_4-H a multiplet (see Table I).

Experimental Section

Melting points were determined in open capillaries and are uncorrected. The purity of the compounds was ascertained by TLC (silica gel-G, BDH, hexane-ethyl acetate, 2:1). IR spectra of compounds were taken in KBr (ν_{max}, cm^{-1}) on Perkin-Elmer FT-IR spectrometer and ^1H NMR spectra in $CDCl_3$ on a varian EM-390 (90 MHz) spectrometer using TMS as an internal standard (chemical shift in δ, ppm). The mass spectra (70 eV) of some of the compounds were obtained on Jeol JMS-D 300 spectrometer. Microanalytical data were obtained from University of Poona, Pune, India.

The dimethyl-2,6-diaryl-4-oxocyclohexane-1,1-dicarboxylates[10] were obtained by the Michael addition of dimethyl malonate to 1,5-diaryl-1,4-pentadien-3-ones. The compounds were purified

Table I—Characterization data of compounds **4a-e** to **9a-e**

Compd.	Yield (%)	m.p. °C	Mol. formula†*	^{1}H NMR (δ, ppm in $CDCl_3$)
4a	70	228-29	$C_{21}H_{21}N_5O_3$	2.85 (dd,2H,7H$_e$&9H$_e$), 3.15 (dd,2H,7H$_a$&9H$_a$), 4.20 (dd,2H,6H&10H), 7.56-7.65 (m,12H,Ar-H&NH$_2$),7.70 (s,1H,CONH), 9.30 (s,2H,NH of 2,3-pyrazolidinedione)
4b	72	215-18	$C_{23}H_{25}N_5O_5$	2.74 (dd,2H,7H$_e$&9H$_e$), 3.12 (dd,2H,7H$_a$&9H$_a$), 3.34 (s,6H,Ar-OC*H*$_3$), 4.24 (dd,2H, 6H&10H), 7.58-7.69 (m,10H,Ar-H&NH$_2$),7.72 (s,1H,CONH), 9.92 (s,2H,NH of 2,3-pyrazolidinedione)
4c	69	220-22	$C_{21}H_{19}Cl_2N_5O_3$	—
4d	72	240-42	$C_{25}H_{31}N_7O_3$	—
4e	70	198-200	$C_{17}H_{17}N_5O_3S_2$	2.82 (dd,2H,7H$_e$&9H$_e$), 3.20 (dd,2H,7H$_a$&9H$_a$), 4.16 (dd,2H,6H&10H), 7.44-7.59 (m,8H, Thiophene-H&NH$_2$), 7.70 (s,2H,CONH), 9.76 (s,2H,NH of 2,3-pyra-zolidinedione)
5a	68	235-37	$C_{21}H_{20}N_4O_4$	2.62 (dd,2H,7H$_e$&9H$_e$), 2.98 (dd,2H,7H$_a$&9H$_a$), 4.15 (dd,2H,6H&10H), 7.50-7.68 (m,12H,Ar-H&NH$_2$),7.75 (s,1H,CONH), 9.82 (s,1H,NH of 2,3-oxazolidinedione)
5b	69	220-21	$C_{23}H_{24}N_4O_6$	—
5c	67	225-28	$C_{21}H_{18}Cl_2N_4O_4$	2.90 (dd,2H,7H$_e$&9H$_e$), 3.22 (dd,2H,7H$_a$&9H$_a$), 4.12 (dd,2H,6H&10H), 7.00-7.42 (m,10H,Ar-H&NH$_2$),7.74 (s,1H,CONH), 9.84 (s,1H,NH of 2,3-oxazolidinedione)
5d	68	210-12	$C_{25}H_{30}N_6O_3$	—
5e	66	202-04	$C_{17}H_{16}N_4O_4S_2$	2.78 (dd,2H,7H$_e$&9H$_e$), 3.14 (dd,2H,7H$_a$&9H$_a$), 4.22 (dd,2H,6H&10H), 7.45-7.60 (m,8H, Thiophene-H&NH$_2$), 7.65 (s,1H,CONH), 9.52 (s,1H,NH of 2,3-oxazolidinedione)
6a	70	146-48	$C_{20}H_{16}N_4O_2Se$	3.25-3.40 (m, 2H, C$_4$-H), 4.10 (t,1H, C$_5$-H), 5.25 (s,1H, C$_7$-H), 7.10-7.50 (m,10H,Ar-H), 9.28 (s,2H,NH of 2,3-pyrazolidinedione)
6b	71	110-13(d)	$C_{22}H_{20}N_4O_4Se$	3.18-3.32 (m, 2H, C$_4$-H), 3.50 (s,6H,Ar-OC*H*$_3$), 4.25 (t,1H, C$_5$-H), 5.28 (s,1H, C$_7$-H), 7.02-7.48 (m,8H,Ar-H), 9.18 (s,2H,NH of 2,3-pyrazolidinedione)
6c	66	138-40	$C_{20}H_{14}Cl_2N_4O_2Se$	—
6d	69	120-22	$C_{24}H_{26}N_6O_2Se$	—
6e	70	129-31	$C_{16}H_{12}N_4O_2S_2Se$	3.24-3.40 (m, 2H, C$_4$-H), 4.20 (t,1H, C$_5$-H), 5.35 (s,1H, C$_7$-H), 7.14-7.52 (m,6H, Thiophene-H), 9.28 (s,2H,NH of 2,3-pyrazolinedione)
7a	70	176-78	$C_{20}H_{15}N_3O_3Se$	3.38-3.52 (m,2H, C$_4$-H), 4.48 (t,1H, C$_5$-H), 5.52 (s,1H, C$_7$-H), 7.20-7.45 (m,10H, Ar-H), 10.35 (s,1H,NH of 2,3-oxazolidinedione)
7b	68	126-28	$C_{22}H_{19}N_3O_5Se$	—
7c	69	165-68	$C_{20}H_{13}Cl_2N_3O_3Se$	3.45-3.60 (m, 2H, C$_4$-H), 4.36 (t,1H, C$_5$-H), 5.48 (s,1H,C$_7$-H), 7.34-7.58 (m,8H, Ar-H),10.40 (s,1H,NH of 2,3-oxazolidinedione)
7d	68	140-42	$C_{24}H_{25}N_5O_3Se$	—
7e	69	130-33	$C_{16}H_{11}N_3O_3S_2Se$	3.42 -3.57 (m,2H, C$_4$-H), 4.37 (t,1H, C$_5$-H), 5.52 (s,1H, C$_7$-H), 7.02-7.38 (m,6H, Thiophene-H),10.42 (s,1H,NH of 2,3-oxazolidinedione)
8a	60	100-03(d)	$C_{20}H_{16}N_4O_2S$	3.28-3.38 (m,2H, C$_4$-H), 4.45 (t,1H, C$_5$-H), 5.32 (s,1H, C$_7$-H), 7.05-7.48 (m,10H, Ar-H),9.25 (s,2H,NH of 2,3-pyrazolidinedione)
8b	63	125-28(B)	$C_{22}H_{20}N_4O_4S$	—
8c	61	115-17	$C_{20}H_{14}Cl_2N_4O_2S$	3.35-3.50 (m, 2H, C$_4$-H), 4.48 (t,1H, C$_5$-H), 5.40 (s,1H, C$_7$-H), 7.15-7.50 (m,8H, Ar-H), 9.30 (s,2H,NH of 2,3-pyrazolidinedione)
8d	63	130-32	$C_{20}H_{25}N_6O_2S$	—
8e	62	142-44	$C_{16}H_{12}N_4O_2S_3$	3.24-3.32 (m, 2H, C$_4$-H), 4.46 (t,1H, C$_5$-H), 5.25 (s,1H, C$_7$-H), 7.00-7.42 (m,6H, Thiophene-H), 9.24 (s,2H,NH of 2,3-pyrazolidinedione)

Contd

Table I—Characterization data of compounds **4a-e** to **9a-e**—*Contd*

Compd	Yield (%)	m.p. °C	Mol. formula†*	^{1}H NMR (δ, ppm in $CDCl_3$)
9a	61	112-14	$C_{20}H_{15}N_3O_3S$	3.35-3.51 (m, 2H, C_4-H), 4.52 (t,1H, C_5-H), 5.65 (s,1H, C_7-H), 7.05-7.34 (m, 10H, Ar-H), 10.34 (s,1H,NH of 2,3-oxazolidinedione)
9b	63	102-05(d)	$C_{22}H_{19}N_3O_5S$	3.28-3.40 (m,2H, C_4-H), 3.46 (s,6H,Ar-OCH_3), 4.44 (t,1H, C_5-H), 5.62 (s,1H, C_7-H), 7.00-7.35 (m,8H,Ar-H),10.32 (s,1H,NH of 2,3-oxazolidinedione)
9c	60	118-20	$C_{20}H_{13}Cl_2N_3O_3S$	—
9d	62	127-29	$C_{24}H_{25}N_5O_3S$	—
9e	60	104-06	$C_{16}H_{11}N_3O_3S_3$	3.37-3.50 (m,2H, C_4-H), 4.58 (t,1H, C_5-H), 5.45 (s,1H, C_7-H), 7.04-7.40 (m,6H,Thiophene-H), 10.30 (s,1H,NH of 2,3-oxazolidinedione)

†Satisfactory microanalyses were obtained for **4a, 4d, 5b, 6a, 6c, 6e, 7b , 8b, 9a** and **9e**: C± 0.24%, H± 0.15%, N ± 0.18%.
*Molecular ions were observed for **4a, 5e, 6e, 7a, 8a** and **9e** at 391, 404, 434, 423, 376 and 389 respectively at 70 eV.

by recrystallization from methanol [**1d**: m.p. 140-41°C, yield 65%. Cal. (Found): C, 69.00 (69.21); H, 7.12 (7.05). **1e**: m.p. 148-49°C, yield 75%. Cal. (Found): C, 57.12 (56.95); H, 4.79 (4.87)].

The 6,10-diaryl-2,3-diazaspiro(4,5)decane-1, 4, 8-triones/6, 10-diaryl-2-oxa-3-azaspiro(4, 5)-decane-1,4,8-triones (**2** and **3**) were prepared by the condensation of **1** with $NH_2NH_2.H_2O$ and $NH_2OH.HCl$[3,4]. The compounds were purified by recrystallization from methanol [**2d**: m.p. 225-27°C, yield 69%. Cal (Found): C, 68.55 (68.35); H, 6.71 (6.78); N, 13.32 (13.50). **2e**: m.p. 199-01°C, yield 70%. Cal (Found): C, 55.47 (55.62); H, 4.07 (4.14). **3d**: m.p. 186-87°C, yield 65%. Cal (Found): C, 68.39 (68.19); H, 6.45 (6.37); N, 9.96 (9.85). **3e**: m.p. 204-06°C, yield 67%. Cal. (Found): C, 55.31 (55.52); H, 3.77 (3.85)].

8-Semicarbazono-6, 10-diaryl-2, 3-diazaspiro-(4,5)decane-1,4-diones/6, 10-diaryl-2-oxa-3-azaspiro(4, 5)decane-1, 4-diones 4/5. General procedure. Semicarbazide hydrochloride (0.017 mole) and sodium acetate trihydrate (0.03 mole) were dissolved in ethanol (40 mL) and the solid, if any, formed was filtered off. To this, compound **2** (0.0029 mole) in ethanol was added and the contents were refluxed for 4-5 hr on a steam-bath. The reaction mixture was then concentrated, cooled and poured onto crushed ice. The separated solid was filtered, washed thoroughly with cold water, dried and recrystallized from ethanol to get pure **4/5**.

5,7-Diarylcyclohexeno[3, 4-*d*]-1-selena-2,3-diazolyl-6-spiro-5'-(2',3'-pyrazolidine/2', 3'-oxazolidine)-1',4'-diones 6/7. General procedure. The semicarbazone **3** (0.0025 mole) in glacial acetic acid (20 mL) was warmed while stirring in order to get a clear solution. Selenium dioxide powder (0.0025 mole) was then added in portions and continued the stirring while maintaining the temperature at 60-70°C until the evolution of gas ceased. The reaction mixture was then allowed to attain room temperature and the deposited selenium was removed by filtration. When the filtrate was poured on crushed ice, a solid product was separated. It was filtered and washed thoroughly with cold water and sodium bicarbonate solution. The product obtained was purified by chromatography.

5,7-Diaryl cyclohexeno[3, 4-*d*]-1-thia-2, 3-diazolyl-6-spiro-5'-(2', 3'-pyrazolidine/2', 3'-oxazolidine)-1',4'-diones 8/9. General procedure. The semicarbazone **3** (0.0025 mole) was added portion-wise to an excess of thionyl chloride (5 mL) maintained at -5 to -10°C and allowed to reach the room temperature where it was kept for a further period of 1-2 hrs. The reaction mixture was diluted with 30 mL of dichloromethane and treated with ice-cold solution of sodium carbonate. The organic layer was separated and washed repeatedly with water and then dried over anhydrous sodium sulfate. Evaporation of the solvent gave a gummy substance which was solidified by triturating with petroleum ether (40-60°). The crude product obtained was purified by column chromatography.

Acknowledgement

One of the authors (MVRR) gratefully acknowledges the authorities of Sri Venkateswara University, Tirupati for the award of "NSRCUI" Research Fellowship.

References

1 Bhaskar Reddy D, Ramana Reddy M V & Padmavathi V, *Indian J Chem*, (in press).
2 Bhaskar Reddy D, Padmavathi V & Padmaja A, *Indian J Heterocyclic Chem*, 2, **1993**, 229.
3 Bhaskar Reddy D, Padmavathi V & Ramana Reddy P V, *Indian J Chem*, 31B, **1992**, 774 and references cited therein.
4 Bhaskar Reddy D, Padmavathi V, Seenaiah B & Ramana Reddy M V, *Org Prep Proced Int*, 24, **1992**, 21.
5 Sharma K S & Sing S P, *Indian J Chem*, 31B, **1992**, 396.
6 Lalezari I, Shafiee A & Yazdani S, *J Pharma Sciences*, 63, **1974**, 628 and references cited therein.
7 Sharma K S, Sarita & Sharda Kumari, *Indian J Chem*, 4, **1994**, 137.
8 Klayman D L & Guntur W H H, *Organic Selenium Compounds, Their Chemistry and Biology* (Washington, New York), **1972**.
9 Shafiee A, Lalezari I, Yazdany S & Pournorouz A, *J Pharm Sciences*, 62, **1973**, 839.
10 Bhaskar Reddy D, Padmavathi V & Muralidhar Reddy M, *Indian J Chem*, 31B, **1992**, 407.